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March 4, 1993

Dr. Jamie Cunliffe
[illegible]

Dear Dr. Cunliffe,

Thank you very much for the new version of your paper. We will not be sending this on to the referees. We are very embarrassed by the length of time our referees have taken with your paper, but have finally obtained a referee's report. I regret to say that it is very negative. I am enclosing part of the report. In general, our referees feel that the paper is far too discursive. I would not advise you to revise the paper in anything like its present form. I return both versions of your paper herewith.

Yours sincerely

[illegible]

Ms 3983: Cunliffe: Morphostasis and Immunity

"Ig supergene like LIGANDs develop to act as a focus on which to grow highly specific gap junctional plates and crfeate developomental compartments. The genes specifying these molecules can now be copied then altered by a "mix and match" process to generate a set of LIGANDs which have a great variability within a herd. These pleomorphic LIGANDs will now act as the final arbiters of healthy self in each individual. Over many meiotic generations, they have eventually evolved into Mhc class I LIGANDs. Newly developed scavenger cells may now be able, when required, to electrically couple with any somatic cell that displays self specific LIGANDs and observe a horror autotoxicus to it. These scavengers need a mechanism to produce and/or select self specific RECEPTORs unique to each ZDC (zygote derived colony). This must be done post-meiotically over a number of mitotic generations - the "generation of specificity". (This possibly coincides with the evolution of amniotic embryos.) These scavengers resemble natural killer cells"

As this passage from pages 26 and 27 of the manuscript show, the author sets great store by "seamlessness", the integration of large areas of biological thinking into what he himself is not ashamed to propose has the promise of a "grand unification theory". I am reminded of the aspirations of Herbert Spencer, who was also not ashamed to attempt the integration of everything in his System of Philosophy. And I am tempted to recall what George Eliot said about Herbert Spencer as well, after a visit with him to Kew Gardens for a "scientific expedition" to test some notions or other, that "if the flowers didn't agree with his theories, why, *tant pis pour les fleurs*!"

The author feels that immunologists are barking up the wrong tree, with all their emphasis on lymphocytes, receptors, major histocompatibility antigens and so on. Or so he says, in no uncertain terms at the beginning of his essay. Surely, he argues, we should concentrate on other criteria by which health and disease are recorded in animal tissues. For reasons which are not absolutely clear to me, he focuses his attention on epithelia, where electrical connectivity is a sign of health, and disconnection evidence of disorder. There is something appealing to him about the fact that gap junctions have holes in them, evidence that cytotoxic mechanisms and normal healthy interactions between cells are seamlessly related to each other (see the Figure appended to the manuscript). Although the manuscript is very long, I do not in fact see any argument as to why the author has selected this attribute as the key marker of health and disease. It just seems to be his idea, that's all. To substantiate his notion that immunologists are missing the point (his phrase), he urges that signals involved in the formation and failure of epithelial connectivity are older in phylogeny than components of the immune system. So what? The immune system is what it is; its evolution is a matter of interest, a lot of conjecture, and increasingly pertinent evidence from lower vertebrates and invertebrates. Let's get on with something small and discriminating and leave the author to his fervid generalizations.